

COMPARATIVE ANALYSIS OF SAFETY, EFFICACY AND FETOMATERNAL OUTCOME OF INDUCTION OF LABOR WITH TABLET MIFEPRISTONE AND TABLET MISOPROSTOL VERSUS TABLET MISOPROSTOL

Ashtekar Archana¹, Chaudhari Shilpa², Gosavi Amrapali³, Warty Tanvi⁴, Singh Manika⁵, Karan Shreya⁶, Sharma Swati⁷

HOW TO CITE THIS ARTICLE:

Ashtekar Archana, Chaudhari Shilpa, Gosavi Amrapali, Warty Tanvi, Singh Manika, Karan Shreya, Sharma Swati. "Comparative Analysis of Safety, Efficacy and Fetomaternal Outcome of Induction of Labor with Tablet Mifepristone and Tablet Misoprostol versus Tablet Misoprostol". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 49, October 02; Page: 11706-11714, DOI: 10.14260/jemds/2014/3538

ABSTRACT: OBJECTIVES: The present study aims at comparing the efficacy, safety and fetomaternal outcome of Misoprostol as cervical ripening and labor inducing agent versus Mifepristone and Misoprostol. The study also aims to observe the improvement in pre induction Bishop's score, proportion of patients going in labor, to study induction-delivery interval. **METHODS:** It is randomized prospective studies conducted on 100 women. Women were randomized in group A and in group B of 50 patients in each group. Group A received tab Mifepristone 200 mg orally on day 1 followed by tablet Misoprostol 25 mcg after 48 hours and continued 4 hrly till patient went in active labor with maximum four tablets and group B patients received tablet Misoprostol 25mcg and continued 25mcg 4hrly till patient went in active labor. **RESULTS:** The study demonstrated significant efficacy of tablet Mifepristone for cervical ripening and induction of labor as pre induction Bishop's score was improved. 32% patients went into labor only with tablet Mifepristone. The mean induction-delivery interval was 9.5 hrs in Group A and 11.78 hrs in Group B, 40% patients delivered by cesarean section in group A but it was not associated with any differences in final neonatal outcome in both the groups. Uterine hyper stimulation was present in 42% patients in group A as compared to only 20% patients in group B. Fetal distress was present in 38% of patients in group A as compared to 18% patients in group B. No any difference in final neonatal outcome was observed in both the groups. **CONCLUSION:** Mifepristone pretreatment is more efficacious and significantly shortens the induction-delivery interval and it has got dual role as a cervical ripening and labor inducing agent.

KEYWORDS: Tablet Mifepristone, Tablet Misoprostol, Induction of labor.

INTRODUCTION: Obstetricians often come across with many conditions and complications where induction of labor is not only indicated but also becomes an important aspect of management specially in cases of ante-partum hemorrhage, eclampsia, intra uterine fetal death, premature rupture of membrane, prolonged pregnancy. When labor is induced, it must end in the birth of a healthy fetus and healthy mother. Un-effaced cervix becomes a major obstacle in induction of labor.

Recently, Misoprostol a PGE1 analogue is being used for inducing labor in patients with unripe cervix. The effectiveness and safety of Misoprostol for induction of labor was accepted by ACOG (1999)¹ and it has reaffirmed the recommendation for use of Misoprostol because of its proven safety and efficacy. Misoprostol is effective in ripening the cervix and hence can be used to induce as well as augment labor process.³

ORIGINAL ARTICLE

Tablet Mifepristone is also called as RU (Roussel Uclaf) - 486. It is a 19 – nor steroid with potent competitive anti-progesterone and significant anti-glucocorticoid activity. Mifepristone is used as a pretreatment to prime the cervix adequately.³

Mifepristone produced a modification in the consistency of the cervix with a statistical improvement in cervical calibration.⁴ Mifepristone causes blockage of progesterone receptors and inhibits the activity of progesterone at cellular level with potent anti progestogenic, anti-glucocorticoid and a weak anti androgenic action and causes cervical ripening effect.⁵ Mifepristone has minimal effects on uterine contractility and increase the sensitivity to prostaglandins and convert the quiet pregnant uterus into organ of spontaneous activity.⁴

Various studies conducted on induction of labor in live term pregnancies with Mifepristone in doses of 200-400mg has shown to improve cervical ripening and rates of induction of labor with no apparent maternal or fetal side effects.^{6,7,8,9} Also some studies have shown that combined Mifepristone with Misoprostol is safe, efficient and economical and convenient induction agent for initiation of labor,¹⁰ but the cesarean section rate was significantly lower in induction with Mifepristone alone but found more with Mifepristone followed by tablet Misoprostol.¹¹

MATERIALS AND METHODS: It is a hospital based prospective randomized comparative study conducted on 100 women with prolonged pregnancy, cephalic presentation, with intact membranes and adequate pelvis fitting in inclusion criteria and with no contraindication to vaginal delivery without any fetomaternal high risk factor. Women attending antenatal clinic, who met the inclusion criteria were enrolled in study. Written informed consent taken from patients.

INCLUSION CRITERIA:

1. Prolonged pregnancy
2. Cephalic presentation
3. Intact membrane
4. Adequate pelvis

EXCLUSION CRITERIA:

1. Previous Lower Segment Cesarean Section (LSCS).
2. Intra Uterine Growth Restriction (IUGR).
3. Oligohydramnios.
4. Malpresentation.
5. Associated medical disorder (hypertension, diabetes mellitus, heart disease, anemia, thyroid, epilepsy, asthma).
6. Premature Rupture of Membrane (PROM).
7. Congenital Anomaly.
8. Hypersensitivity to Prostaglandins & Mifepristone.
9. Preeclampsia, Eclampsia.
10. Placental insufficiency.
11. Cephalo Pelvic Disproportion.

The women were randomized in group A and group B of 50 in each group.

ORIGINAL ARTICLE

METHOD OF STUDY: GROUP A PATIENT: It consists of 50 patients .They received T. Mifepristone 200mg orally on day 1 which is followed by T. Misoprostol 25 mcg sublingual or orally after 48 hrs and continued 4 hrly till patient goes in active labor with maximum four tablets.

GROUP B PATIENTS: It consists of 50 patients. They received T. Misoprostol 25 mcg sublingual or oral and continued 25 mcg 4 hrly till patient went in active labor with maximum four tablets. After admission in ward, initial information about the study was given and a written informed consent was taken. As mentioned above they were randomized in Group A and Group B.

After history taking, general and systemic examination was done. Obstetric examination was done to reassure lie, gestation age, and fetal heart rate. Per vaginal examination was done to assess Bishop's score and to assess pelvis. Patient was subjected to non-stress test (NST). Ultrasonography was done for interval growth, amniotic fluid index and to exclude any fetal high risk factor.

In Group A patient digital per vaginal examination was conducted at the beginning of induction and Bishop's score was recorded. After administration of T. Mifepristone 200mg orally patient was not allowed to go home. After 24 hrs NST was repeated and per vaginal examination done under all aseptic precaution to note Bishop's score.

Then after 48 hrs T. Misoprostol 25 mcg sublingual or oral every 4 hrly till patient went in active labor up to maximum four tablets. Maternal vital parameters like pulse, blood pressure, uterine contractions and strict fetal heart rate (FHR) monitoring was done by stethoscope and by cardiotocography. Re-assessment was done to note:

1. Improvement of Bishop's score.
2. Progression of labor.

Patient was asked about side effects of drugs like vomiting, fever or diarrhea, pain in abdomen, fainting, fatigue. Checked for per vaginal bleeding or per vaginal leaking if present. FHR monitoring was done every 15 min in first stage of labor and every 5 min in second stage of labor to confirm fetal wellbeing. A per vaginum examination was done 4hrly in active labor to reassess Bishop's score. Uterine contractions were strictly monitored to see whether any uterine tachysystole or hypertonia was present.

IN GROUP B PATIENTS: As mentioned above after noting Bishop's score T. Misoprostol 25 mcg sublingual or oral was given and was repeated 4hrly till patient went in active labor. The course of labor was monitored. Strictly FHS monitoring was done every 15 minutes in first stage of labor and in second stage every 5 minutes. If any supplementary drug was required to augment labor was given and recording of same done.

Mode of delivery was studied. After delivery APGAR score of baby was noted and recorded.

The detailed analysis was carried out for both the groups regarding the.

1) Efficacy of drugs in terms of:

- Change in Bishop's score after 6 hours and after 12 hours.
- Induction – delivery interval.
- No of doses of T. Misoprostol required.
- Oxytocin augmentation if required.
- Number of failure of induction of labor.

ORIGINAL ARTICLE

2) Maternal outcome studied in terms of:

- Incidence of uterine hyper stimulation in terms of tachysystole or hypertonus.
- Mode of delivery.
- Incidence of cesarean delivery.
- Adverse effect of drug after intake.

The two main outcomes measured were the number of women going into labor within 48 hrs of T. Mifepristone administration and in those whether cervical ripening with T. Mifepristone significantly reduced the time from T. Misoprostol administration to delivery compared with the use of only T. Misoprostol alone in group B.

3) Fetal outcome studied in terms of:

- APGAR score.
- Needed admission in neonatal intensive care unit (NICU).

RESULTS: Following observations are found from the present study: Association done by χ^2 test and $p < 0.05$ was considered significant.

	Group	Bishop's score Mean	Std. Deviation
Pre induction	A	4.50	0.88
	B	4.72	0.88
After 6 hours of drug	A	6.80	1.42
	B	5.94	1.39
After 12 hours of drug	A	8.22	1.20
	B	7.81	1.93

Table 1: Change in Bishop's score

Mean pre-induction Bishop's score was 4.50 in Group A. It was increased by 6.80 in 6 hrs and 8.22 after 12 hrs. The mean pre induction Bishop's score was 4.72 in Group B. It was increased by 5.94 in 6 hrs and 7.81 after 12 hrs. So it is found that Bishop's score is significantly improved in Group A with T. Mifepristone with T. Misoprostol than only with T. Misoprostol in Group B which was statistically significant.

Gravida	Group A		Group B	
	Mean (hrs)	Std. Deviation	Mean (hrs)	Std. Deviation
Primigravida	10.50	5.189	13.83	3.985
Multigravida	8.68	2.950	9.88	3.421
T	1.43		3.77	
P	P<0.05 significant (S)		P<0.001 Highly significant(HS)	

Table 2: Induction – Delivery Interval with Gravid status

ORIGINAL ARTICLE

The mean Induction–delivery interval in Primigravidae in Group A was 10.50 hrs while in Multigravida was 8.68 hrs. While in Primigravidae in Group B was 13.83 hrs and in multigravida was in 9.88 hrs. The Induction Delivery interval in multigravida is less in both the groups than primigravidae.

Mode of Delivery	Group		Total
	Group A N= 50	Group B N=50	
Instrumental	1	3	4
LSCS	20	5	25
Vaginal	29	42	71
Total	50	50	100

Table 3: MODE OF DELIVERY

$$\chi^2 = 10.45 \text{ DF}=1 \text{ P}<0.001 \text{ HS}$$

In Group A, 16 patients delivered by only T. Mifepristone out of which 11 are delivered vaginally and 5 by emergency cesarean section. In Group A, total 20 patients i.e.40% are delivered by cesarean section and 29 i.e. 58% are delivered vaginally and 1 patient required instrumental (forceps) delivery.

In Group B, 5 patients i.e. 10 % required cesarean section and 42 (84%) delivered spontaneously vaginally and 3 patients required instrumental (2 forceps and 1 vacuum) delivery. So incidence of cesarean section is found more in Group A than Group B which is significant.

Group	Induction Delivery Interval Mean hrs	Std. Deviation
A	9.59	4.27
B	11.78	4.17

Table 4: Comparison of Efficacy of Drug

$$P<0.05 \text{ S}$$

The Mean Induction – delivery interval was 9.59 hrs in Group A and in Group B, it was 11.78 hrs. It means that induction delivery interval duration is less in Group A (T. Mifepristone with T. Misoprostol) than in Group B with T. Misoprostol.

Uterine Hyperactivity	Group A N=50	Group B N=50
Hyper stimulation	22	10

Table 9: Incidence of Uterine Hyperactivity

$$\chi^2 = 5.56 \text{ df}=1 \text{ P}<0.05 \text{ Significant.}$$

ORIGINAL ARTICLE

The hyper stimulation was present in 22 (44%) patients in Group A with T. Mifepristone with T. Misoprostol as compared to 10(20%) patients in Group B with T. Misoprostol. It is found to be statistically significant.

	Group	N	Mean	Std. Deviation
APGAR score <8at 1 min	A	7	6.43	.976
	B	6	7.00	.632

Table 10: Neonatal outcome

P>0.05 NS

The incidence of birth asphyxia was similar in both the groups. In Group A only 7 babies and in Group B only 6 babies had their APGAR score < 8 whereas in rest all babies the APGAR score was good.

Fetal distress	Group		Total
	Group A	Group B	
No	31	41	72
Yes	19	9	28
Total	50	50	100

Table 12

$\chi^2 = 4.96$, $df=1$ $P < 0.05$ Sig

The fetal distress was present in 19 (38%) cases in Group A with T. Mifepristone with T. Misoprostol while it was present in only 9(18%) cases in Group B with T. Misoprostol which is statistically found to be significant.

DISCUSSION: In this study we found significant improvement in Bishops score in group A (T. Mifepristone with T. Misoprostol) compare with Group B (T. Misoprostol) this suggests that tab. Mifepristone has got dual role as cervical ripening agent and also as labor inducing agent .This drug causes reduction in induction –delivery interval.

Study done by Wing DA et al⁸ showed induction–delivery interval less with use of T. Mifepristone than in placebo subjects. Present study found p value <0.05, which showed statistically significant. (Table 2) Other observation in present study showed that dose of T. Misoprostol required in pre-treated patient with T. Mifepristol was less. In our study 32% women in Group A went in labor without T. Misoprostol.

Stenlund PM et al¹² found 79.2% women went in labor without T. Misoprostol, Another study by Su H et al⁹ states that 22.58% women went in labor without T. Misoprostol. J McGill et al¹¹ found 66% women went in labor without T. Misoprostol. Elliot CL et al⁷ found in their conclusion that T. Mifepristol is known to cause softening and dilatation of cervix and increase in uterine activity. Lil L et al¹⁰ found Bishops score was higher in women induced with T. Mifepristol.

ORIGINAL ARTICLE

Present study also showed significant improvement in Bishop's score in Group A with T. Mifepristone with T. Misoprostol than only with T. Misoprostol in Group B which was statistically significant. (Table 1)

In present study 32% women went in labor only with T. Mifepristone and out of it 69% had vaginal delivery and 31% underwent cesarean section. Remaining 68% Women required Misoprostol for induction of labor .Out of that 56% delivered virginally, which quite low compare to study is done by Li L¹⁰ who found 80% delivered vaginally.44% required cesarean section. J. McGill¹¹ found rate of cesarean section was higher in women who required T. Mifepristol followed by T. Misoprostol.

The hyper stimulation was present in 44% women in Group A with T. Mifepristone and T. Misoprostol as compare to 20% women in Group B with T. Misoprostol. It is found to be statistically significant .There is a study showing increase in incidence of tachysystole, hypertonia and fetal heart sound abnormality in women treated with T. Mifepristol with prostaglandins.¹³ There was no significant difference in neonatal outcome of both groups.

The result of present study shows that T. Mifepristol is a simple and effective treatment for inducing labor in post term pregnancy with unripe cervix. Li L et al ¹⁰ concluded that T. Mifepristol combined with T. Misoprostol is safe, efficient, economical and convenient induction agent for initiation of labor.

Our study concludes that incidence of cesarean section is more in group where T. Misoprostol used followed by T. Mifepristol. T. Mifepristol as inducing agent in case of previous caesarean delivery also proved to be safe according to study done by Lelaider.¹⁴ In present study post cesarean patients were in exclusion criteria. Compare to dinoprostone as labor induction drug T. Mifepristone is proved as better drug.¹⁵ Weeks et al¹⁶ studied misoprostol for induction of labor when used in low doses is as effective as vaginal dinoprostol with no excess of uterine hyperstimulation.

CONCLUSION: Thus from this study it can be concluded that T Mifepristone is efficacious agent for cervical ripening and for initiation of labor. But when it is combined with T. Misoprostol there is increase in number of uterine hyper stimulation, increase in fetal distress and increase in rate of cesarean deliveries.

REFERENCES:

1. William's Obstetrics Williams Obstetrics, 23rd ed, Chapter 22. Labour Induction; 500.
2. Fletcher HM, Mitchell S, Simeon D, Frederick J, Brown D. Intravaginal Misoprostol as a cervical ripening agent. BJOG: An international Journal of Obstetrics and Gynaecology.1993; 100: 641-4.
3. Frydman R, Baton C, Lelaidier C, Vial M, Bourget P, Fernandez H. Mife prystone for induction of labour. Lancet.1991; 337 (8739): 488-9.
4. Frydman R, Fernandez H, Pons J, Ulmann A. Mifepristol (RU 486) and therapeutic late pregnancy termination: a double -blind studyof two different doses. Hum. Reprod. 1988; 3 (6): 803-6s.
5. Newhall EP, Winik of B. American journal of obstetrics and Gynecology. Abortion with Mifepristol and Misoprostol: Regimens, efficacy, acceptability and future directions.2000; 183 (2): S44- 3.
6. Clark K, Ji H, Feltovich H, Janowski J., Carroll C, Chien EK .Am J Obstet Gynecol. Mifepristone – induced cervical ripening: structural, biomechanical and molecular event. 2006; 194: 1391-8.

ORIGINAL ARTICLE

7. Elliot CL, Brennand JE, Calder AA. The effects of Mifepristone on cervical ripening and labor induction in primigravidae. *Obstet Gynecol.* 1998; 92 (5): 804-9.
8. Wing DA, Fassett MJ, Mishell DR. Mifepristone for pre induction cervical ripening beyond 41 weeks gestation: a randomized controlled trial. *Obstet Gynecol.* 2000; 96 (4): 543-8.
9. Su H, Li E, Weng L. Mifepristone for labour induction. *Zhonghua Fu Chan Ke Za Zhi.*1996; 31 (11): 676-80.
10. Li L,Gao W,Chen S. Labour induction in women at term with Mifepristone and Misoprostol. *Zhonghua Fu Chan Ke Za Zhi.*1996; 31 (11): 681-4.
11. J McGill, Shetty A. Mifepristone and Misoprostol in the induction of labour at term. *International Journal of Gynaecology and Obstetrics.* 2007; 96: 80-84.
12. Stenlund P M, Ekman G, Aedo A R, Bygdeman M. Induction of labor with mifepristone--a randomized, double-blind study versus placebo. *Acta obstetricia et gynecologica Scandinavica.*1999; 78(9):793-6
13. Giacalone PL, Daurés JP, Faure JM, Boulot P, Hedon B, Laffargue F .The effects of mifepristone on uterine sensitivity to oxytocin and on fetal heart rate patterns. *Eur J Obstet Gynecol Reprod Biol.* 2001; 97(1): 30-4.
14. Lelaider C, Baton C, Benifla JL, Fernandez H, Bourger P, Frydman R .Mifepristone for labour induction after previous cesarean section. *British Journal of Obstetrics and Gynecology.* 1994; 101 (6): 501-3.
15. Gaikwad V, Mittal B, Puri M .Comparative analysis of safety, efficacy and fetomaternal outcome of induction of labour with Mifepristone versus intracervical dinoprostone gel. *Research journal of Pharmaceutical, Biological and chemical Sciences.*2014; 5(2):611-6.
16. Weeks A, Alfirevic Z, Faundes A, Hofmeyr GJ, Safar P, Wing D. Misoprostol for induction of labour on a live baby. *International journal Of Obstetrics and Gynecology.* 2007; 99: S194-7.

AUTHORS:

1. Ashtekar Archana
2. Chaudhari Shilpa
3. Gosavi Amrapali
4. Warty Tanvi
5. Singh Manika
6. Karan Shreya
7. Sharma Swati

PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of Obstetrics & Gynaecology, Dr. D. Y. Patil Medical College, Pune, Maharashtra, India.
2. Professor, Department of Obstetrics & Gynaecology, Shrimati Kashibai Nawale Medical College and General Hospital, Nahre, Pune Maharashtra, India.
3. Professor, Department of Obstetrics & Gynaecology, Dr. D. Y. Patil Medical College, Pune, Maharashtra, India.
4. Resident, Department of Obstetrics & Gynaecology, Dr. D. Y. Patil Medical College, Pune, Maharashtra, India.

5. Resident, Department of Obstetrics & Gynaecology, Dr. D. Y. Patil Medical College, Pune, Maharashtra, India.
6. Resident, Department of Obstetrics & Gynaecology, Dr. D. Y. Patil Medical College, Pune, Maharashtra, India.
7. Resident, Department of Obstetrics & Gynaecology, Dr. D. Y. Patil Medical College, Pune, Maharashtra, India.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Chaudhari Shilpa
Professor, Department of OBG,
Shrimati Kashibai Nawale Medical College and
General Hospital, Nahre,
Pune Maharashtra, India.
Email: drshilpachaudhari@yahoo.com

Date of Submission: 05/09/2014.

Date of Peer Review: 06/09/2014.

Date of Acceptance: 25/09/2014.

Date of Publishing: 30/09/2014.